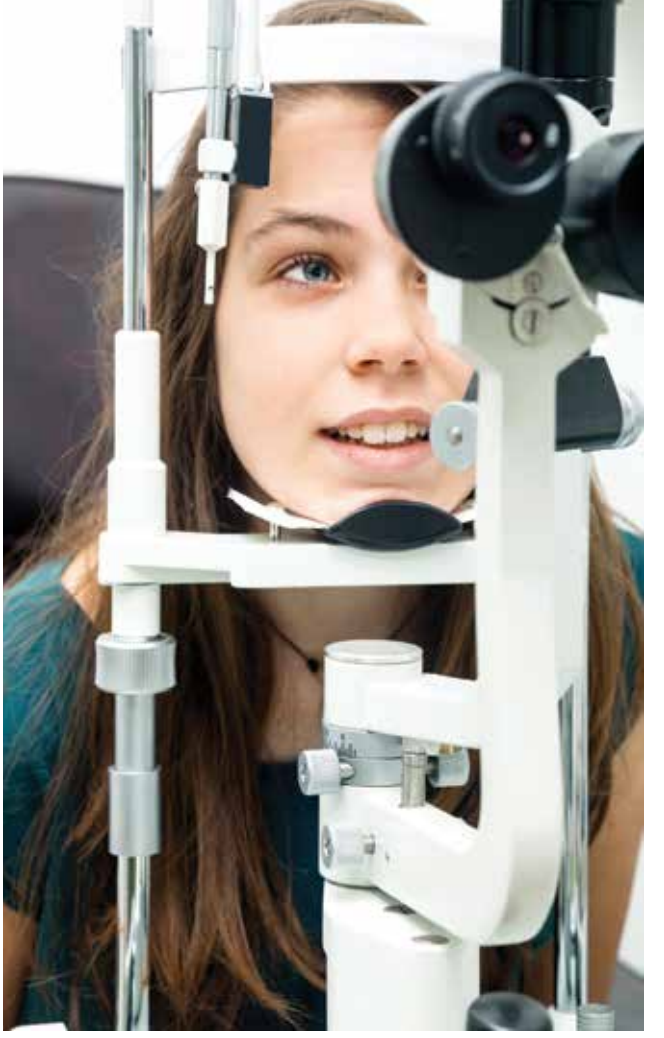
Reducing the future risk of diabetic retinopathy
in young people with type 1 diabetes

MARIA E. CRAIG MB BS, PhD, FRACP, MMed(ClinEpid)

A decline in the incidence of retinopathy in adolescents with type 1 diabetes has occurred in recent decades in parallel with increased use of multiple daily injection therapy and insulin pumps but only a modest decline in HbA_{1c}. Intervention trials that are currently underway may shed further light on strategies to reduce the future risk of retinopathy in young people with type 1 diabetes.



© MAICA/ISTOCKPHOTO. MODEL USED FOR ILLUSTRATIVE PURPOSES ONLY

Key points

- **Diabetic retinopathy is the most serious ocular complication of type 1 diabetes.**
- **Risk factors for development of diabetic retinopathy include diabetes duration, elevated HbA_{1c}, hypertension, nephropathy and dyslipidaemia.**
- **Assessment for retinopathy should be performed by an ophthalmologist or a trained experienced observer through the patient's dilated pupils.**
- **Screening for retinopathy should be performed annually from the age of 10 years (or at onset of puberty if this is earlier), after five years of diabetes duration. Screening should be commenced after two years of diabetes duration in pubertal children.**

ENDOCRINOLOGY TODAY 2015; 4(2): 25-27

Professor Craig is Senior Staff Specialist at the Institute of Endocrinology and Diabetes, The Children's Hospital at Westmead, Sydney, NSW.

How is retinopathy defined?

Diabetic retinopathy progresses through distinct stages, from early nonproliferative retinal changes to proliferative disease marked by neovascularisation of the retina.[1]

Nonproliferative (background) retinopathy is characterised by the presence of microaneurysms, retinal haemorrhages, hard exudates (resulting from protein and lipid leakage), cotton wool spots (microinfarction), and intraretinal microvascular abnormalities including dilatation, constriction and tortuosity of vessels (Figure 1). It is classified as mild (microaneurysms only), moderate (more than just microaneurysms) and severe; all stages are generally asymptomatic. Mild and moderate nonproliferative retinopathy are not vision threatening. Severe nonproliferative retinopathy, which is vision threatening, is characterised by progressive intraretinal microvascular abnormalities and ischaemia, with retinal nerve fibre infarctions (which manifest as cotton wool spots). At all stages of nonproliferative diabetic retinopathy, there is a risk of macular oedema (retinal thickening located within two disc diameters of the centre of the macula, due to capillary leak in the macular or perimacular region). Macular oedema is rare in young people, but is also vision threatening.

Proliferative diabetic retinopathy is characterised by neovascularisation in the retina and/or vitreous posterior surface (Figure 2). This can result in rupture or bleeding of vessels into the vitreoretinal space, which is vision threatening. Advanced proliferative diabetic retinopathy can result in fibrosis and adhesions, which can lead to haemorrhage and retinal detachment.[2]

Figure 1. Nonproliferative diabetic retinopathy with microaneurysms and retinal haemorrhages.

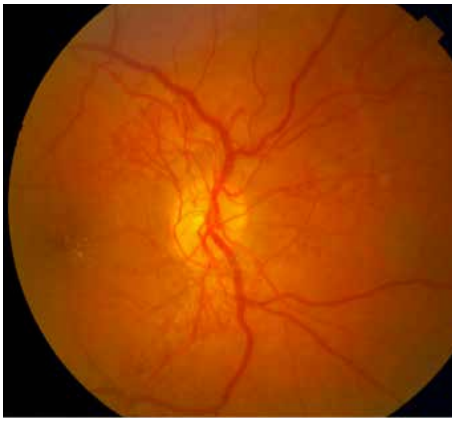


Figure 2. Proliferative diabetic retinopathy with neovascularisation.

1. Risk factors for development of diabetic retinopathy[2,5,6]

- Diabetes duration
- Chronic hyperglycaemia
- High blood pressure/hypertension
- High cholesterol levels/ dyslipidaemia
- High body mass index
- Family history

Epidemiology and risk factors for retinopathy

Diabetic retinopathy is the most serious ocular complication of type 1 diabetes and is the leading cause of acquired blindness in working aged adults, most commonly as a result of macular oedema. Almost all individuals with type 1 diabetes demonstrate some form of diabetic retinopathy 20 years after diagnosis; however, clinically evident retinopathy is uncommon in young people with type 1 diabetes. Nevertheless, subclinical functional and structural abnormalities, including measures of retinal vascular geometry, may be present a few years after the onset of the disease and predict subsequent retinopathy.[3] Furthermore, onset of type 1 diabetes during childhood and adolescence (age <15 years) is associated with a twofold higher risk of progression to vision-threatening retinopathy, particularly in those with poor glycaemic control, compared with an older onset of diabetes (age 15 to 40 years).[4]

The strongest predictor of diabetic retinopathy is duration of diabetes, whereas older age, chronic hyperglycaemia (characterised by persistently elevated HbA_{1c}), hypertension, nephropathy, higher body mass index and dyslipidaemia (particularly cholesterol) are established risk factors (see Box 1).[1,2,5,6] Family history of diabetes complications also increases the risk for retinopathy.[7]

The incidence of retinopathy is lower in children before puberty than during puberty. In an incident cohort of young people from NSW with a median diabetes duration of six years, retinopathy was present in 12% of prepubertal children versus 29% of those in puberty.[8] Younger age of type 1 diabetes onset, particularly before puberty, is associated with a longer diabetes duration before onset of retinopathy;[9] however, in the long term this initial advantage disappears as young onset diabetes does not appear to 'protect' from retinopathy beyond adolescence.

In recent decades, there has been a decline in diabetic retinopathy in young people. In adolescents at a median age of 16 years and diabetes duration of nine years, retinopathy declined from 53% in 1990 to 1994 to 12% in 2005 to 2009.[10] In parallel, HbA_{1c} declined from 9.1 to 8.5% and use of a multiple daily injection regimen (MDI) or insulin pump therapy increased from 17 to 88%. In multivariable analysis, factors associated with a higher risk of retinopathy in this population included treatment with one or two injections per day (versus use of MDI or insulin pumps) and socioeconomic disadvantage, along with established risk factors (such as longer diabetes duration, older age, higher HbA_{1c} and higher systolic blood pressure)[10] In subgroup analysis, there was some evidence that insulin pump therapy conferred additional protection over MDI, with a 50% reduction in the odds of retinopathy in patients treated with insulin pumps, although this did not reach statistical significance ($p = 0.07$).[10] The decline in retinopathy, and other complications, has occurred in parallel with major changes in diabetes management, including intensification of therapy, introduction of modern insulins, identification of modifiable risk factors for retinopathy and more widespread screening for microvascular complications including retinopathy.

How can retinopathy be prevented?

The landmark Diabetes Control and Complications Trial (DCCT) provided clear evidence that intensive diabetes treatment and the associated improved glycaemic control significantly reduce the risk of retinopathy (and other complications) compared with conventional treatment.[11] In the adolescent cohort (aged 13 to 17 years), the risk and progression of background retinopathy was reduced by 53% in the intensive treatment arm (HbA_{1c} 8.1%) compared with conventional treatment (HbA_{1c} 9.8%).[12]

Assessment of retinopathy

The most sensitive detection methods for retinopathy screening are bimicroscopic fundus slit examination through dilated pupils performed by an ophthalmologist or optometrist (who is knowledgeable and experienced in diagnosing diabetic retinopathy) and 7-field stereoscopic retinal photography through dilated pupils.[2] The latter is often used in tertiary diabetes complications screening programs and in research, but may not be available in other settings. Retinal photography with remote reading by experts has potential in areas where qualified eye care professionals are not readily available.[5] However, subsequent review of the patient by an ophthalmologist or optometrist is essential when photos are

not of acceptable quality or for follow up if abnormalities are detected. It should be noted that photos cannot substitute for a comprehensive eye examination, and this should be considered at least initially to detect cataracts or major refractive errors. Results of eye examinations should be documented and transmitted to the referring healthcare professional.[5]

Does the patient require referral to a specialist?

Recent international guidelines from the International Society for Pediatric and Adolescent Diabetes[2] recommend that screening for retinopathy in children and adolescents with type 1 diabetes should be performed annually from the age of 10 years or at onset of puberty if this is earlier. Screening should commence after five years of diabetes duration in prepubertal children or those aged less than 10 years, whereas screening should begin after two years of diabetes duration in pubertal children (see Box 2).[2,5]

How is diabetic retinopathy managed?

The major interventions for retinopathy, when detected in young people, are optimisation of glycaemic and blood pressure control and laser therapy. Optimisation of glycaemic and blood pressure control is also recommended to reduce the risk of developing retinopathy as well as to slow the progression.[1,2,5]

For sight-threatening proliferative diabetic retinopathy, which is rare in young people, laser therapy (also known as panretinal photocoagulation) is recommended. Laser therapy is not indicated for mild or moderate nonproliferative retinopathy. In adults with proliferative diabetic retinopathy, laser therapy reduces the progression of visual loss by more than 50%. There is also evidence in normotensive, normoalbuminuric adults that antihypertensive therapy with an angiotensin II receptor antagonist may provide additional protection against diabetic retinopathy, but to date there are no data in children. The Adolescent Type 1 Diabetes Cardio-Renal Intervention Trial (AdDIT), an international multicentre trial (which includes five sites in Australia),[13] is currently underway and will provide important information on the effect of angiotensin converting enzyme inhibitors and/or statins on the risk of retinopathy, as well as microalbuminuria and cardiovascular outcomes.

What is the role of the GP?

Childhood and adolescence are periods during which intensive education and treatment may prevent or delay the onset and progression of complications including retinopathy. The GP has an important role in:

- providing education to families about the risk factors for diabetic retinopathy (and other complications)
- facilitating screening for retinopathy (when patients are unable to access tertiary diabetes complications screening programs)
- supporting intensive diabetes management, particularly during the crucial period of adolescence when glycaemic control often deteriorates.

2. Recommendations for screening, monitoring and treatment of diabetic retinopathy*[2]

- Screening should be performed annually from age 10 years (or at onset of puberty if this is earlier) after two to five years of diabetes duration (Grade E).
- Screening should be more frequent if there are high-risk features for visual loss. For people with a diabetes duration of less than 10 years, minimal background retinopathy on fundus photography and reasonable glycaemic control, biennial assessment by fundal photography can occur (Grade E).
- Assessment for retinopathy should be performed by an ophthalmologist or a trained experienced observer through dilated pupils (Grade B).
- Initial eye examination should also be considered to detect cataracts or major refractive errors (Grade E).
- In patients with longstanding poor glycaemic control, when control is improved, ophthalmological monitoring is recommended before initiation of intensive treatment and at three-month intervals for six to 12 months thereafter. This is because of potential worsening of retinopathy, particularly if its severity is at or past the moderate nonproliferative stage at the time of intensification (Grade E).
- Laser treatment reduces the rate of visual loss for individuals with vision-threatening retinopathy (Grade A).

Note: Evidence grading levels (A to E) are according to the American Diabetes Association Guidelines.[5]
* From the International Society for Pediatric and Adolescent Diabetes (ISPAD).

The standard of care for management of people with type 1 diabetes is a multidisciplinary team approach, which includes the GP.[14] The improved outcomes for young people with type 1 diabetes in recent years reinforce the importance of early, ongoing and regular referral of patients to specialist centres with expertise in managing paediatric diabetes to safely optimise blood glucose control and reduce the risk of retinopathy.

Conclusion

Diabetic retinopathy is a serious microvascular complication of type 1 diabetes, with prevalence strongly related to duration of diabetes and hyperglycaemia. Although its frequency appears to have deceased in adolescents in recent years, it is the most common cause of new cases of blindness among adults. Screening for early signs of retinopathy during childhood and adolescence enables targeting of modifiable risk factors and intervention. **ET**

References

A list of references is included in the website version (www.medicinetoday.com.au) of this article.

COMPETING INTERESTS: None.

Reducing the future risk of diabetic retinopathy in young people with type 1 diabetes

MARIA E. CRAIG MB BS, PhD, FRACP, MMed(ClinEpi)

References

1. Mohamed Q, Gillies MC, Wong TY. Management of diabetic retinopathy: a systematic review. JAMA 2007; 298: 902-916.
2. Donaghue KC, Wadwa RP, Dimeglio LA, et al. Microvascular and macrovascular complications in children and adolescents. Pediatr Diabetes 2014; 15 Suppl 20: 257-269.
3. Benitez-Aguirre P, Craig ME, Sasongko MB, et al. Retinal vascular geometry predicts incident retinopathy in young people with type 1 diabetes: a prospective cohort study from adolescence. Diabetes Care 2011; 34: 1622-1627.
4. Hietala K, Harjutsalo V, Forsblom C, Summanen P, Groop PH, Group FS. Age at onset and the risk of proliferative retinopathy in type 1 diabetes. Diabetes Care 2010; 33: 1315-1319.
5. Standards of medical care in diabetes--2015: summary of revisions. Diabetes Care 2015; 38 Suppl: S4.
6. Yau JW, Rogers SL, Kawasaki R, et al. Global prevalence and major risk factors of diabetic retinopathy. Diabetes Care 2012; 35: 556-564
7. Soergel M, Kirschstein M, Busch C, et al. Oscillometric twenty-four-hour ambulatory blood pressure values in healthy children and adolescents: a multicenter trial including 1141 subjects. J Pediatr 1997; 130: 178-184.
8. Donaghue KC, Craig ME, Chan AK, et al. Prevalence of diabetes complications 6 years after diagnosis in an incident cohort of childhood diabetes. Diabet Med 2005; 22: 711-718.
9. Donaghue KC, Fairchild JM, Craig ME, et al. Do all prepubertal years of diabetes duration contribute equally to diabetes complications? Diabetes Care 2003; 26: 1224-1229.
10. Downie E, Craig ME, Hing S, Cusumano J, Chan AK, Donaghue KC. Continued reduction in the prevalence of retinopathy in adolescents with type 1 diabetes: role of insulin therapy and glycemic control. Diabetes Care 2011; 34: 2368-2373.
11. DCCT Research Group (Diabetes Control and Complications Trial Research Group). The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993; 329: 977-986.
12. DCCT Research Group (Diabetes Control and Complications Trial Research Group). Effect of intensive diabetes treatment on the development and progression of long-term complications in adolescents with insulin-dependent diabetes mellitus: Diabetes Control and Complications Trial. J Pediatr 1994; 125: 177-188.
13. Cho YH, Craig ME, Davis EA, et al. Cardiac autonomic dysfunction is associated with high-risk albumin-to-creatinine ratio in young adolescents with type 1 diabetes in AdDIT (Adolescent Type 1 Diabetes Cardio-Renal Interventional Trial). Diabetes Care 2015; 38: 676-681.
14. Craig ME, Twigg SM, Donaghue KC, et al. National evidence-based clinical care guidelines for type 1 diabetes in children, adolescents and adults. Canberra: Australian Government Dept of Health and Ageing, 2011.